as a white solid. ^{1}H NMR (500 MHz): δ 1.55 (s, br, 1), 3.71 (s, 4), 3.80 (s, 6), 6.84 (d, 4, J = 8.7), 7.22 (d, 2, J = 8.7).

Benzyl-*p*-methoxybenzylamine. Purification by Kügelrohr distillation afforded 612 mg (74%) of benzyl-*p*-methoxybenzylamine as a clear, colorless oil. Bp: 130 °C at 0.20 Torr. ^{1}H NMR (250 MHz): δ 1.47 (s, br, 1), 3.75 (s, 2), 3.83 (s, 5), 6.85 (d, 2), 7.20–7.50 (m, 7).

Bis(*p*-cyanobenzyl)amine. Purification by silica gel column chromatography using hexane–EtOAc 1:1 as eluent afforded 250 mg (50%) of bis(*p*-cyanobenzyl)amine as a light yellow solid. Mp: 99–100 °C. ^{1}H NMR (400 MHz): δ 1.70 (s, br, 1), 3.86 (s, 4), 7.46 (d, 4, J = 8.3), 7.61 (d, 4, J = 8.3). ^{13}C NMR (100 MHz): δ 52.69, 110.99, 118.87, 128.62, 132.30, 145.50.

Bis[*p*-(trifluoromethyl)benzyl]amine. Purification by silica gel column chromatography using hexane–EtOAc 5:1 as eluent afforded 92 mg (48%) of bis[*p*-(trifluoromethyl)benzyl]amine as a clear, colorless oil. Bp: 120 °C at 0.10 Torr. ^{1}H NMR (400 MHz): δ 1.66 (s, br, 1), 3.87 (s, 4), 7.47 (d, 4, J = 8.0), 7.59 (d, 4, J = 8.0). ^{13}C NMR (100 MHz): δ 52.65, 123.41, 125.36, 125.40, 125.44, 128.32, 144.19. R_f = 0.50 (hexane–EtOAc 3:1).

Benzyl-*p*-(trifluoromethyl)benzylamine. Purification by silica gel chromatography using hexane–EtOAc 4:1 as eluent afforded 866 mg (81%) of benzyl-*p*-(trifluoromethyl)benzylamine as a clear, colorless oil. ^{1}H NMR (400 MHz): δ 1.7 (s, br, 1), 3.8 (s, 2), 3.9 (s, 2), 7.3–7.7 (m, 9).

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Supplementary Material Available: Complete listings of infrared spectra for most of the compounds reported in this paper, and ^{1}H NMR spectra of compounds **8**, **10** (and its trans isomer), **23**, **25**, **31**, **32**, benzyl-5-pentenylamine, benzyl-2-propynylamine, bis(*p*-methoxybenzyl)amine, benzyl-*p*-methoxybenzylamine, and benzyl-*p*-(trifluoromethyl)benzylamine (16 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Syntheses and Ion Selectivity of All Conformational Isomers of Tetrakis((ethoxycarbonyl)methoxy)calix[4]arene

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We have found that the conformer distribution in tetra-O-alkylation of 5,11,17,23-tetra-*tert*-butylcalix[4]-arene-25,26,27,28-tetrol by ethyl bromoacetate is remarkably affected by the metal cation present in the base. In general, the cone conformer predominantly results when the base contains template metal cations whereas the partial-cone and 1,3-alternate conformers result when the base contains nontemplate metal cations. In acetone solvent one can realize the change from the 100% cone selectivity to the 100% partial-cone selectivity. By combining the metal template effect with a protection–deprotection method with a benzyl group, we developed synthetic routes to all of the four conformers. Two-phase solvent extraction established that the cone conformer shows Na^+ selectivity whereas the remaining three conformers show K^+ selectivity. ^{1}H NMR studies established that the 1,3-alternate conformer can form both a 1:1 and a 2:1 metal/calixarene complex and the two metal-binding sites display negative allostericity. This paper thus demonstrates that the metal selectivity of ionophoric calix[*n*]aryl esters can be changed not only by the change in the ring size but also by the conformational change.

Introduction

Calixarenes have been used as a useful basic skeleton for the synthesis of lipophilic,[1-3] water-soluble,[4-6] and ionophoric receptors.[7-12] For the molecular design of these functionalized calixarenes, modification of OH groups arranged on the lower rim is most convenient.[13,14] In particular, much attention is being devoted toward the molecular design of calix[4]arene-based ionophores because of their high ion affinity and high ion selectivity; for example, 5,11,17,23-tetra-*tert*-butyl-25,26,27,28-tetrakis-((ethoxycarbonyl)methoxy)calix[4]arene with a cone conformation (cone-**2a**), readily prepared by the reaction of 5,11,17,23-tetra-*tert*-butylcalix[4]arene-25,26,27,28-tetrol (**1a**) and ethyl bromoacetate in the presence of NaH, shows high Na^+ affinity and high Na^+ selectivity which are comparable with those of cryptand 222.[7-11] Recently, we found that tetra-O-alkylation of **1a** with alkyl bromide (e.g., *n*-PrBr) yields a mixture of conformational isomers, and the conformer distribution is profoundly affected by alkali or alkaline earth metal ions present in the base.[15-17] We

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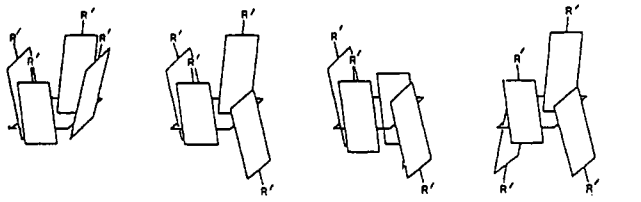
Table I. Conformer Distribution for the Reaction of 1a or 1b with Ethyl Bromoacetate[a]

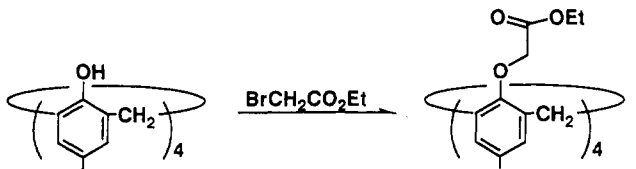
calix[4]arene	base (equiv for 1)	solvent	temp (°C)	time (h)	yield (%)	conformer distribution in 2 (%)		
						cone	partial cone	1,3-alternate
1a	NaH (16)	THF	67	1	96	100	0	0
1a	Li_2CO_3 (20)	DMF	70	45	22	100	0	0
1a	Na_2CO_3 (20)	DMF	70	6	100	88	12	0
1a	K_2CO_3 (20)	DMF	70	8	100	84	16	0
1a	Cs_2CO_3 (20)	DMF	70	3	100	27	73	0
1a	Li_2CO_3 (20)	acetone	56	45	0[b]	0	0	0
1a	Na_2CO_3 (20)	acetone	56	22	59	100	0	0
1a	K_2CO_3 (20)	acetone	56	22	99	96	3	0
1a	Cs_2CO_3 (20)	acetone	56	1	100	0	100	0
1b	K_2CO_3 (20)	acetone	56	24	100	33	46	21
1b	Cs_2CO_3 (20)	acetone	56	12	100	6	38	56

[a] In all runs 1,2-alternate-2 was not detected. [b] The product is a 1,3-di-O-substituted calix[4]arene distal isomer.

also found that the reaction of 5,11,17,23-tetra-*tert*-butyl-25,27-dihydroxy-26,28-bis(2-pyridylmethoxy)calix[4]-arene with ethyl bromoacetate in the presence of K_2CO_3 yields three conformational isomers (cone, partial cone, and 1,3-alternate) of 5,11,17,23-tetra-*tert*-butyl-25,27-bis((eth-



oxycarbonyl)methoxy)-26,28-bis(2-pyridylmethoxy)calix-[4]arene in a 79:16:5 ratio.[12] These findings suggest that also in **2a** one may be able to synthesize conformational isomers other than cone.[18] To the best of our knowledge, however, the compounds reported so far are limited to cone-**2a** and its cone analogs.[7-11] This situation tempted



a:R=t-Bu
b:R=H

us to exploit new synthetic methods for the conformational isomers other than cone. If one can synthesize them, it is of particular interest to know the ion affinity and ion selectivity of these new conformational isomers. As potential strategies for the syntheses, we employed the metal template effect and the protection–deprotection method using a benzyl group which were known to be effective in the syntheses of conformational isomers of tetra-O-alkylcalix[4]arenes.[15,16,19]

Experimental Section

Materials. Compound **1a** was synthesized according to Gutsche's method.[20] This compound was de-*tert*-butylated to **1b**.[21] From **1a**, cone and partial-cone isomers of **2a** could be directly synthesized by the reaction with ethyl bromoacetate. From **1b**, on the other hand, cone, partial-cone, and 1,3-alternate isomers of **2b** could be directly synthesized. Other isomers were synthesized according to a protection–deprotection method.

General Method for the Direct Synthesis of 2 from 1. Compound **1a** (containing 1 mol of toluene in the crystal, 1.0 g; 1.35 mmol) in 40 mL of solvent was treated with excess ethyl bromoacetate (4.51 g; 27 mmol) in the presence of appropriate base (see Table I). The conformer distribution was estimated by HPLC analysis (column Zorbax ODS (ϕ 4.6 × 250 mm), chloroform:methanol = 1:4 v/v). In a separate study, each conformer was isolated by a preparative TLC method (silica gel, *n*-hexane:ethyl acetate = 1:4 v/v) and the structures were determined from the splitting pattern of the $ArCH_2Ar$ methylene protons in ^1H NMR spectroscopy.[13] Since the $EtOCOCH_2$ group is bulky enough to inhibit the oxygen-through-the-annulus rotation,[15,16] **2a** is conformationally immobile at room temperature. The analytical data for cone-**2a** were described in the literature.[7-11] Partial-cone-**2a**: mp 203–205 °C; IR (Nujol) $\nu_{C=O}$ 1750 cm^{-1}, no ν_{OH}; ^1H NMR ($CDCl_3$, 25 °C) δ 1.01, 1.34, and 1.38 (*t*-Bu, s each, 18 H, 9 H, and 9 H, respectively), 1.16, 1.30, and 1.33 (CH_3, t each, 3 H, 6 H, and 3 H, respectively), 3.13, 3.85, 3.91, and 4.50 ($ArCH_2Ar$, d each, 2 H each), 4.01 and 4.19–4.30 ($COOCH_2$, q and m, respectively, 2 H and 6 H, respectively), 4.37, 4.38, 4.44, and 4.45 (OCH_2CO, s, d, s, and d, respectively, 2 H each), 6.49, 7.04, 7.05, and 7.40 (ArH, d, d, s, and s, respectively, 2 H each). Anal. Calcd for $C_{60}H_{80}O_{12}$: C, 72.55; H, 8.12. Found: C, 72.52; H, 8.08.

Cone, partial-cone, and 1,3-alternate isomers of **2b** were synthesized in a manner similar to that described above. Cone-**2b**: mp 91–92 °C; IR (Nujol) $\nu_{C=O}$ 1755 cm^{-1}, no ν_{OH}; ^1H NMR ($CDCl_3$, 25 °C) δ 1.29 (CH_3, t, 12 H), 3.24 and 4.87 ($ArCH_2Ar$, d each, 4 H each), 4.21 ($COOCH_2$, q, 8 H), 4.73 (OCH_2CO, s, 8 H), 6.61–6.66 (ArH, m, 12 H). Anal. Calcd for $C_{44}H_{48}O_{12}$: C, 68.74; H, 6.29. Found: C, 68.69; H, 6.11. 1,3-Alternate-**2b**: mp 111–112 °C; IR (Nujol) $\nu_{C=O}$ 1760 cm^{-1}, no ν_{OH}; ^1H NMR ($CDCl_3$, 25 °C) δ 1.33 (CH_3, t, 12 H), 3.79 (OCH_2CO, s, 8 H), 4.04 ($ArCH_2Ar$, s, 8 H), 4.25 ($COOCH_2$, q, 8 H), 6.72 and 7.14 (ArH, t and d, respectively, 4 H and 8 H, respectively). Anal. Calcd for $C_{44}H_{48}O_{12}$: C, 68.74; H, 6.29. Found: C, 68.62; H, 6.14.

We also isolated partial-cone-**2b**. The product (oil) showed the ^1H NMR spectrum which is consistent with a partial-cone conformation: ^1H NMR ($CDCl_3$, 25 °C) δ 1.22, 1.29, and 1.35 (CH_3, t each, 6 H, 3 H, and 3 H, respectively), 3.17, 3.76, 3.89, and 4.39 ($ArCH_2Ar$, d each, 2 H each), 4.02, 4.26, 4.38, and 4.46 (OCH_2CO, s, s, d, and d, respectively, 2 H each), 4.04 and 4.20–4.35 ($COOCH_2$, q and m, respectively, 2 H and 6 H, respectively), 6.23, 6.49, 6.88, 6.98, 7.10, 7.14, and 7.49 (ArH, d d, t, t, t, d d, d, and d, respectively, 2 H, 2 H, 1 H, 1 H, 2 H, 2 H, and 2 H, respectively). We could not crystallize this compound, however. We thus did not use this compound for the ion extraction studies.

25-(Benzyloxy)-26,27,28-tris((ethoxycarbonyl)methoxy)-5,11,17,23-tetra-*tert*-butylcalix[4]arene (4a). 25-(Benzyloxy)-26,27,28-trihydroxy-5,11,17,23-tetra-*tert*-butylcalix[4]arene (**3a**) (7.0 g; 9.45 mmol)[16] was treated with ethyl bromoacetate (20.8 mL; 189 mmol) in anhydrous acetone at the reflux temperature for 1 h in the presence of Cs_2CO_3 (61.6 g; 189 mmol) under a

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nitrogen stream. After filtration, the filtrate was diluted with water and extracted with chloroform. The organic layer was dried over $MgSO_4$ and concentrated to dryness. The residual solid (two spots on the TLC plate) was subjected to column chromatography (silica gel, chloroform). **4a**(Bzl$^{\alpha}$Es$^{\alpha}$Es$^{\alpha}$Es$^{\beta}$):[35] mp 189–190 °C, yield 39%; IR (Nujol) $\nu_{C=O}$ 1758 cm^{-1}, no ν_{OH}; ^{1}H NMR ($CDCl_3$, 25 °C) δ 1.02, 1.03, 1.14, and 1.33 (*t*-Bu, s each, 9 H each), 1.13, 1.28, and 1.32 (CH_3, t each, 3 H each), 3.12, 3.15, 3.68, 3.83, 3.87, 3.89, 4.42, and 4.50 ($ArCH_2Ar$, d each, 1 H each), 3.88–4.02 and 4.14–4.29 ($COOCH_2$, m each, 2 H and 4 H, respectively), 4.22, 4.35, 4.36, 4.39, 4.40, and 4.43 (OCH_2CO, d each, 1 H each), 4.72 (OCH_2Ar, s, 2 H), 6.49, 6.53, 7.02, 7.04, 7.05, 7.09, and 7.34 (ArH, d, d, d, d, s, d, and d, respectively, 1 H, 1 H, 1 H, 1 H, 2 H, 1 H, and 1 H, respectively), 7.33–7.38 and 7.49–7.51 (BzlH, m each, 3 H and 2 H, respectively). Anal. Calcd for $C_{63}H_{80}O_{10}$: C, 75.87; H, 8.08. Found: C, 75.96; H, 8.06. From the splitting pattern of the $ArCH_2Ar$ methylene protons the conformation of this compound is assigned to partial cone. If the ester group distal to the benzyl group is inverted, two different ester peaks should appear in a 1:2 integral intensity ratio. In fact, however, we counted three different ester peaks. This supports the view that the ester group proximal to the benzyl group is inverted (i.e., Bzl$^{\alpha}$Es$^{\alpha}$Es$^{\alpha}$Es$^{\beta}$).[36] **4a**(Bzl$^{\alpha}$Es$^{\beta}$Es$^{\alpha}$Es$^{\beta}$): mp 239–240 °C, yield 31%; IR (Nujol) $\nu_{C=O}$ 1760 cm^{-1}, no ν_{OH}; ^{1}H NMR ($CDCl_3$, 25 °C) δ 0.96, 1.23, and 1.25 (*t*-Bu, s each, 18 H, 9 H and 9 H, respectively), 1.19 and 1.28 (CH_3, t each, 6 H and 3 H, respectively), 3.50, 3.58, and 4.06 (OCH_2CO, d, d and s, respectively, 2 H, 2 H, and 4 H, respectively), 3.66, 3.95, and 4.02 ($ArCH_2Ar$, d, s, and d, respectively, 2 H, 4 H, and 2 H, respectively), 4.08 and 4.19 ($COOCH_2$, q each, 4 H and 2 H, respectively), 4.58 (OCH_2Ar, s, 2 H), 6.69, 7.07, 7.11, and 7.12 (ArH, d, d, s, and s, respectively, 2 H each), 6.73–6.76 and 7.10–7.15 (BzlH, m each, 2 H and 3 H, respectively). Anal. Calcd for $C_{63}H_{80}O_{10}$: C, 75.87; H, 8.08. Found: C, 76.03; H, 8.06. From the splitting pattern of the $ArCH_2Ar$ methylene protons the conformation is assigned to 1,3-alternate. An integral intensity ratio of the ester groups also supports this assignment.

25-Hydroxy-26,27,28-tris((ethoxycarbonyl)methoxy)-5,11,17,23-tetra-*tert*-butylcalix[4]arene (5a). Compound **4a** (3.50 g; 3.51 mmol) in chloroform (175 mL) was treated with Me_3SiBr (0.46 mL; 3.51 mmol) at room temperature for 1 h under a nitrogen stream. The solution was diluted with water, and the organic layer was separated. After being dried over $MgSO_4$ the solution was concentrated to dryness. The residue was recrystallized from chloroform–ethanol. **5a**(OH$^{\alpha}$Es$^{\alpha}$Es$^{\alpha}$Es$^{\beta}$) (product from **4a**(Bzl$^{\alpha}$Es$^{\alpha}$Es$^{\alpha}$Es$^{\beta}$)): mp 168–169 °C; yield 97%; IR (Nujol) ν_{OH} 3470 cm^{-1}, $\nu_{C=O}$ 1758 and 1770 cm^{-1}; ^{1}H NMR ($CDCl_3$, 25 °C) δ 0.97, 1.11, 1.32, and 1.33 (*t*-Bu, s each, 9 H each), 1.25, 1.27, and 1.34 (CH_3, t each, 3 H each), 3.21, 3.22, 3.69, 3.76, and 3.86 ($ArCH_2Ar$, d each, 1 H each), 4.13–4.42 ($ArCH_2Ar$, $COOCH_2$, and OCH_2CO, m, 3 H, 6 H, and 4 H, respectively), 4.65 and 5.11 (OCH_2CO, d each, 1 H each), 6.50, 6.65, 6.92, 7.12, 7.13, 7.18, 7.21, and 7.37 (ArH, d each, 1 H each), 7.10 (OH, s, 1 H). Anal. Calcd for $C_{56}H_{74}O_{10}$: C, 74.48; H, 8.11. Found: C, 74.04; H, 8.22. **5a**(OH$^{\alpha}$Es$^{\alpha}$Es$^{\beta}$Es$^{\alpha}$) (product from **4a**(Bzl$^{\alpha}$Es$^{\beta}$Es$^{\alpha}$Es$^{\beta}$)): mp 189–190 °C; yield 98%; IR (Nujol) ν_{OH} 3435 cm^{-1}, $\nu_{C=O}$ 1740 and 1765 cm^{-1}; ^{1}H NMR ($CDCl_3$, 25 °C) δ 1.04, 1.31, and 1.34 (*t*-Bu, s each, 18 H, 9 H, and 9 H, respectively), 1.18 and 1.29 (CH_3, t each, 3 H and 6 H, respectively), 3.20, 3.96, and 4.13 ($ArCH_2Ar$, d, br s, and d, respectively, 2 H, 4 H, and 2 H, respectively), 3.76, 4.35, and 4.63 (OCH_2CO, s, d, and d, respectively, 2 H each), 4.07 and 4.23 ($COOCH_2$, q each, 2 H and 4 H, respectively), 6.36 (OH, s, 1 H), 6.76, 7.02, 7.04, and 7.35 (ArH, d, s, d, and s, respectively, 2 H each). Anal. Calcd for $C_{56}H_{74}O_{10}$: C, 74.48; H, 8.11. Found: C, 74.02; H, 8.19.

5a(OH$^{\alpha}$Es$^{\alpha}$Es$^{\alpha}$Es$^{\alpha}$) was synthesized according to the following method. Compound **1a** (1.0 g; 1.35 mmol) was treated with ethyl bromoacetate (2.98 mL; 27 mmol) in anhydrous DMF (20 mL) at room temperature for 12 h in the presence of BaO (4.14 g; 27 mmol) under a nitrogen stream. After filtration, the filtrate was diluted with water and extracted with chloroform. The organic layer was dried over $MgSO_4$ and concentrated to dryness. The residue was recrystallized from chloroform–ethanol. **5a**-(OH$^{\alpha}$Es$^{\alpha}$Es$^{\alpha}$Es$^{\alpha}$): mp 168–169 °C; yield 78%; IR (Nujol) ν_{OH} 3530 cm^{-1}, $\nu_{C=O}$ 1760 cm^{-1}; ^{1}H NMR ($CDCl_3$, 25 °C) δ 0.86, 1.27, and 1.28 (*t*-Bu, s each, 18 H, 9 H, and 9 H, respectively), 1.26 and 1.34 (CH_3, t each, 3 H and 6 H, respectively), 3.24, 3.25, 4.34, and 4.94 ($ArCH_2Ar$, d each, 2 H each), 4.14 and 4.24–4.32 ($COOCH_2$, q and m, respectively, 2 H and 4 H, respectively), 4.50, 4.68, and 5.07 (OCH_2CO, d, d and s, respectively, 2 H each), 6.58, 6.60, 7.01, and 7.07 (ArH, d, d, s, and s, respectively, 2 H each), 6.81 (OH, s, 1 H). Anal. Calcd for $C_{56}H_{74}O_{10}$: C, 74.14; H, 8.22. Found: C, 73.64; H, 8.14.

1,2-Alternate-2a and 1,3-Alternate-2a. Compound **5a** (3.0 g; 3.31 mmol) was treated with ethyl bromoacetate (7.29 mL; 66.1 mmol) in anhydrous acetone (25 mL) at reflux temperature for 1 h in the presence of Cs_2CO_3 (21.5 g; 66.1 mmol) under a nitrogen stream. The workup is similar to that described for partial-cone-**2a**. The HPLC analysis taught us that the product from **5a**(OH$^{\alpha}$Es$^{\alpha}$Es$^{\alpha}$Es$^{\beta}$) is a mixture of partial-cone-**2a** and unknown compound A (50:50 ratio) whereas the product from **5a**-(OH$^{\alpha}$Es$^{\alpha}$Es$^{\beta}$Es$^{\alpha}$) is a mixture of partial-cone-**2a** and unknown compound B (65:35 ratio). The physical properties of these compounds were very similar to each other, and the isolation by column chromatography or preparative TLC was extremely difficult. We expected that if these compounds showed different affinities for Na^+, they might be isolated by fractional recrystallization in the presence of $NaClO_4$. We recrystallized the product (200 mg; 0.20 mmol) from **5a**(OH$^{\alpha}$Es$^{\alpha}$Es$^{\alpha}$Es$^{\beta}$) from ethanol in the presence of $NaClO_4$ (25 mg; 0.20 mmol). The crystals thus isolated were partial-cone-**2a** (95% purity). The filtrate was partially concentrated and cooled. Compound A thus isolated was identified to be 1,2-alternate-**2a** (100% purity) on the basis of the following analyses. Partial-cone-**2a** (as $NaClO_4$ complex): mp 263–266 °C, yield 43%; IR (KBr disk) $\nu_{C=O}$ 1725, 1740, and 1750 cm^{-1}; ^{1}H NMR ($CDCl_3$, 25 °C) 1.12, 1.19, and 1.39 (CH_3, t each, 3 H 3 H, and 6 H, respectively), 1.14, 1.26, and 1.34 (*t*-Bu, s each, 18 H, 9 H, and 9 H, respectively), 3.09, 4.45, 4.47, and 4.59 (OCH_2CO, s, s, d, and d, respectively, 2 H each), 3.40, 3.83, 4.09, and 4.33 ($ArCH_2Ar$, d each, 2 H each), 3.98, 4.16 and 4.29–4.46 ($COOCH_2$, q, q, and m, respectively, 2 H, 2 H, and 4 H, respectively), 7.02, 7.17, 7.20, and 7.21 (ArH, d, d, s, and s, respectively, 2 H each). Anal. Calcd for $C_{60}H_{80}O_{12}$·$NaClO_4$: C, 64.59; H, 7.23. Found: C, 64.48; H, 7.25. The elemental analysis data support that partial-cone-**2a** is isolated as the $NaClO_4$ complex. 1,2-Alternate-**2a**: mp 180–181 °C; yield 41%; IR (KBr disk) $\nu_{C=O}$ 1730 and 1760 cm^{-1}; ^{1}H NMR ($CDCl_3$, 25 °C) δ 1.19 (CH_3, t, 12 H), 1.25 (*t*-Bu, s, 36 H), 3.23, 4.10, and 4.71 ($ArCH_2Ar$, d, s, and d, respectively, 2 H, 4 H, and 2 H, respectively), 3.85 and 4.05 (OCH_2CO, d each, 4 H each), 4.00–4.15 ($COOCH_2$, m, 8 H), 7.04 and 7.14 (ArH, d each, 4 H each). Anal. Calcd for $C_{60}H_{80}O_{12}$: C, 72.55; H, 8.12. Found: C, 72.24; H, 8.04. The elemental analysis data show that 1,2-alternate-**2a** is isolated as a salt-free calix-[4]arene.

We applied a similar fractional recrystallization method to the product from **5a**(OH$^{\alpha}$Es$^{\alpha}$Es$^{\beta}$Es$^{\alpha}$) but failed. We dissolved the mixture and 10 equiv of $NaClO_4$ in ethanol and then evaporated the solution to dryness. The solid residue was washed with chloroform several times, and the insoluble solid was recovered. The ^{1}H NMR analysis established that compound B thus obtained has a 1,3-alternate conformation. 1,3-Alternate-**2a**: mp 264–265 °C; yield 17%; IR (KBr disk) $\nu_{C=O}$ 1740 and 1760 cm^{-1}; ^{1}H NMR ($CDCl_3$, 25 °C) δ 1.22 (CH_3, t, 12 H), 1.22 (*t*-Bu, s, 36 H), 3.66 (OCH_2CO, s, 8 H), 4.02 ($ArCH_2Ar$, s, 8 H), 4.11 ($COOCH_2$, q, 8 H), 7.10 (ArH, s, 8 H). Anal. Calcd for $C_{60}H_{80}O_{12}$: C, 72.55; H, 8.12. Found: C, 72.38; H, 8.08.

Solvent Extraction. Two-phase solvent extraction was carried out between water (5 mL, [alkali picrate] = 2.50×10^{-4} M, [MOH] = 0.10 M, [MCl] = 0.50 M) and dichloromethane (5 mL, [calix-[4]arene] = 2.50×10^{-3} M). The two-phase mixture was shaken for 30 min at 25 °C. We confirmed that this period is enough to attain the distribution equilibrium. The extractability was determined spectrophotometrically from the decrease in the absorbance of the picrate ion in the aqueous phase.

Results and Discussion

Metal Template Effects on the Direct Synthesis of Conformational Isomers. As reported previously,[7–11] the reaction of **1a** with ethyl bromoacetate in the presence of NaH gave cone-**2a** in quantitative yield (Table I). In order

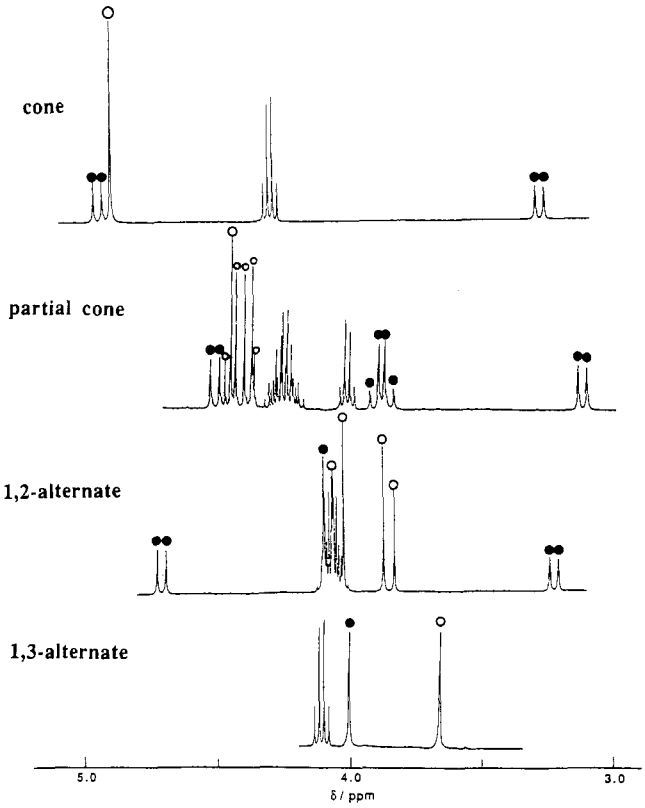


Figure 1. Partial ^1H NMR spectra of the four conformers of **2a** (1.0×10^{-3} M): $CDCl_3$, 25 °C, 400 MHz. The filled circles denote the $ArCH_2Ar$ methylene protons and the open circles denote the OCH_2CO methylene protons.

to estimate the metal template effect, we used alkali carbonates as base because the Li^+, Na^+, K^+, and Cs^+ salts are commercially available. In DMF solvent the "perfect" cone selectivity was observed for Li_2CO_3. On the other hand, when Na_2CO_3, K_2CO_3, or Cs_2CO_3 was used as base, we recognized a new spot on the TLC plate. It is known that the conformational characteristics of calix[4]arenes are conveniently estimated by the splitting pattern of the $ArCH_2Ar$ methylene protons in ^1H NMR spectroscopy.[13] Although cone-**2a** should give a pair of doublets with a large chemical shift difference, the new spot resulted in a pair of doublets with a large chemical shift difference (3.13 and 4.50 ppm) and another pair of doublets with a small chemical shift difference (3.85 and 3.91 ppm; 400 MHz, 25 °C, $CDCl_3$: Figure 1). This splitting pattern is consistent with a partial-cone conformation. As shown in Table I, the yield of partial-cone-**2a** increased in the order of $Na_2CO_3 < K_2CO_3 < Cs_2CO_3$. The more remarkable metal template effect was observed for the reaction of **1a** with ethyl bromoacetate in acetone. The tetra-O-substitution reaction did not proceed in the presence of Li_2CO_3. The "perfect" cone selectivity was observed for Na_2CO_3 whereas the "perfect" partial-cone selectivity was observed for Cs_2CO_3. It is surprising that the conformer distribution changes from 100% cone to 100% partial cone only by the change in the alkali metal cations.

Why is this reaction so sensitively affected by the added metal cations? Cone-**2a** shows high affinity toward Na^+.[7-11] Hence, it is reasonable to consider that when ethyl bromoacetate attacks **1a** or partially-O-substituted **1a**, it strongly undergoes the metal template effect;[15-17] that is, the (ethoxycarbonyl)methyl groups tend to be immobilized in a cone conformation through the interaction between Na^+ and the OCH_2CO groups. This explanation may be extended to the Li^+ ion. In contrast, Cs^+ is scarcely bound to cone-**2a**.[7-11] The results in Table I indicate that, in the absence of the metal template effect, partial-cone-**2a** becomes a major product. When comparing acetone with DMF, the ion pairs in acetone have the tight nature and the interaction between M^+ and the OCH_2CO group is relatively strong. This is why the more conspicuous metal template effect was observed for acetone.

Why, then, does this reaction tend to yield partial-cone-**2a** in the absence of the metal template effect? On the basis of the previous studies on the conformational analysis of calix[4]arenes, we can offer two possible reasons. The first one is the steric effect. According to Gutsche,[13] $\Delta\delta$ between H_{exo} and H_{endo} in the $ArCH_2Ar$ methylene protons serves as a measure of the "flattening" of each phenyl unit: $\Delta\delta$ is generally 0.9 ppm for a system in the regular cone conformation and in the "flattened" conformation $\Delta\delta$ is significantly decreased.[13] $\Delta\delta$ in **1a** is 0.76 ppm whereas that in cone-**2a** is increased up to 1.8 ppm (400 MHz, 25 °C, $CDCl_3$). The change implies that the phenyl rings in cone-**2a** become more or less parallel to each other because of the steric crowding on the narrow lower rim. We consider that the steric crowding is reduced (at least, partially) by inversion of a phenyl unit. This view is supported by the X-ray crystallographic studies on calix[4]arene derivatives with a partial-cone conformation.[15,21]

The second reason is related to an electrostatic effect. Careful examination of X-ray crystallographic pictures of a cone-**2a** analogue teaches us that in an uncomplexed calix[4]arene four carbonyls are turned outward (exo-annulus direction) presumably to reduce electrostatic repulsion among carbonyl groups whereas in a metal-complexed calix[4]arene they are turned inward (endo-annulus direction) to bind M^+ in the cavity.[22] One can thus consider that the electrostatic repulsion can also be reduced by inversion of a phenyl unit.

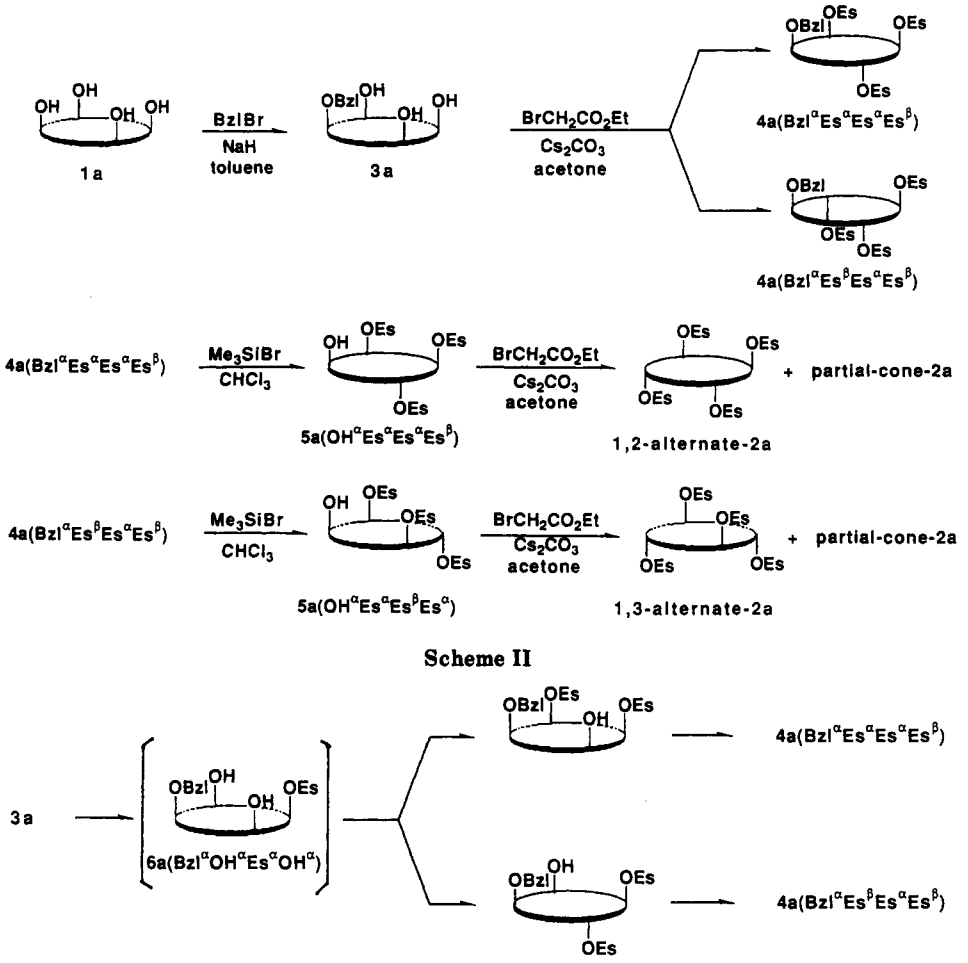
Although these effects may explain the formation of partial-cone-**2a** in preference to cone-**2a**, they do not explain why neither 1,2-alternate-**2a** nor 1,3-alternate-**2a** is formed. In order to fully understand the final conformer distribution in **2a**, we must investigate the conformer distribution at each O-substitution step as we previously employed in O-alkylation of **1a**.[15,16] We will discuss this problem later again.

The last question which arises from Table I is related to the difference in the conformer distribution between **2a** and **2b**. As shown in Table I, only cone and partial-cone result from **1a** whereas these isomers and 1,3-alternate result from **1b**. We recently estimated the steric energies of tetra-O-methylated **1a** and **1b** using molecular mechanics (MM3).[23] The computational results show that introduction of *t*-Bu groups into the para positions increases the steric crowding in cone, partial cone, and 1,2-alternate but not in 1,3-alternate. In cone and 1,2-alternate, the conformations are thus destabilized by the *t*-Bu groups. In partial cone the potential surface near the energy minimum is rather flattened, so the increased steric crowding can be relaxed through the conformational change. In 1,3-alternate, on the other hand, the four phenol units are parallel to each other, so that introduced *t*-Bu groups do not increase the steric crowding. The results allow us to predict that introduction of *t*-Bu groups will increase partial cone and 1,3-alternate and decrease cone and 1,2-alternate. Examination of Table I reveals

(22) Grootenhuis, P. D. J.; Kollman, P. A.; Groenen, L. C.; Reinhoudt, D. N.; van Hummel, G. J.; Ugozzoli, F.; Andreetti, G. D. *J. Am. Chem. Soc.* **1990**, *112*, 4165.

(23) Harada, T.; Rudzinski, J. M.; Shinkai, S. *J. Chem. Soc., Perkin Trans. 2*, in press. Extensive computational studies were reported by Grootenhuis et al.[22] but the influence of the *t*-Bu groups on tetra-O-methylated **1a** or **1b** is not discussed.

Scheme I



Scheme II

that this prediction is borne out. In acetone in the presence of K_2CO_3, for example, cone is decreased from 96% to 33% whereas partial cone and 1,3-alternate are increased from 3% and 0% to 46% and 21%, respectively. Clearly, the influence of the *t*-Bu groups is rationalized in terms of the steric effect.

Syntheses of 1,2-Alternate-2a and 1,3-Alternate-2a by a Protection–Deprotection Method. 1,2-Alternate-**2a** and 1,3-alternate-**2a** could not be synthesized directly by the reaction of **1a** and ethyl bromoacetate. We thus utilized a protection–deprotection method using a benzyl group.[15,16,19] These conformational isomers could be synthesized according to the reaction route shown in Scheme I. Compound **1a** was monobenzylated to give **3a**.[16,24,25] The reaction of **3a** with ethyl bromoacetate in acetone in the presence of Cs_2CO_3 as base yielded **4a**($Bzl^{\alpha}Es^{\alpha}Es^{\alpha}Es^{\beta}$) with a partial-cone conformation and **4a**($Bzl^{\alpha}Es^{\beta}Es^{\alpha}Es^{\beta}$) with a 1,3-alternate conformation in a 50:50 ratio owing to facile inversion of one or two phenol units. The benzyl group was removed with Me_3SiBr. The regenerated OH group was reacted with ethyl bromoacetate in the presence of Cs_2CO_3. The facile inversion of the phenol unit took place again and 1,2-alternate-**2a** or 1,3-alternate-**2a** resulted. As shown in Figure 1, the $ArCH_2Ar$ methylene protons in 1,2-alternate-**2a** gave a pair of doublets with a large chemical shift difference (4.71 and 3.23 ppm) and a singlet resonance (4.10 ppm: 400 MHz, 25 °C, $CDCl_3$) and those in 1,3-alternate-**2a** gave a characteristic singlet resonance because of its high symmetry. These results indicate that the protection–deprotection method is recommended as a useful strategy for the synthesis of these conformational isomers.

Table II. Conformer Distribution for the Reaction of 5a and Ethyl Bromoacetate[a]

conformn of starting **5a**	conformer distribution in **2a** (%)			
	cone	partial cone	1,2-alternate	1,3-alternate
$OH^{\alpha}Es^{\alpha}Es^{\alpha}Es^{\alpha}$	0	100	0	0
$OH^{\alpha}Es^{\alpha}Es^{\alpha}Es^{\beta}$	0	50	50	0
$OH^{\alpha}Es^{\alpha}Es^{\beta}Es^{\alpha}$	0	65	0	35

[a] **5a** (2.7 g; 2.98 mmol), Cs_2CO_3 (19.4 g; 59.5 mmol), $BrCH_2COOEt$ (6.57 mL; 59.5 mmol) in acetone (20 mL) at the reflux temperature for 1 h.

How Is the Conformation Immobilized? To obtain further insights into the metal template effects, we tried the reaction of several lower substituted intermediates with ethyl bromoacetate in the presence of Cs_2CO_3. As we established previously, the oxygen-through-the-annulus rotation is allowed for the OH group in any lower substituted calix[4]arenes and the position is governed by the thermodynamic stability.[15,16] Thus, three conformational isomers can exist in tri-O-substituted calix[4]arene.[16] We thus carried out the reaction of three **5a**(OHEsEsEs) conformers with ethyl bromoacetate in the presence of Cs_2CO_3. As summarized in Table II, **5a**($OH^{\alpha}Es^{\alpha}Es^{\alpha}Es^{\alpha}$) with a cone conformation yielded only partial-cone-**2a**. On the other hand, **5a**($OH^{\alpha}Es^{\alpha}Es^{\alpha}Es^{\beta}$) and **5a**($OH^{\alpha}Es^{\alpha}Es^{\beta}Es^{\alpha}$) with a partial-cone conformation yielded both 1,2-alternate-**2a** and 1,3-alternate-**2a**, respectively, in addition to partial-cone-**2a**. As mentioned above, the direct reaction

(24) Calestani, G.; Ugozzoli, F.; Arduini, A.; Ghidini, E.; Ungaro, R. *J. Chem. Soc., Chem. Commun.* **1987**, 344.
(25) Groenen, L. C.; Ruel, B. H. M.; Casnati, A.; Verboom, W.; Pochini, A.; Ungaro, R.; Reinhoudt, D. N. *Tetrahedron* **1991**, *47*, 8379.

of **1a** with ethyl bromoacetate in the presence of Cs_2CO_3 yields only partial-cone-**2a**. The results in Table II thus establish that the direct reaction includes only **5a**-($OH^{\alpha}Es^{\alpha}Es^{\alpha}Es^{\alpha}$) as an intermediate. It is now clear, therefore, that the rotation of a phenol unit to give partial-cone-**2a** occurs when the fourth ester enters.

The reaction step from **3a** to **4a** in Scheme I is rewritten more in detail as in Scheme II. We have confirmed by ^1H NMR spectroscopy that when 1 mol of **3a** is reacted with 1 mol of ethyl bromoacetate, the ester group enters into the distal position to give **6a**($Bzl^{\alpha}OH^{\alpha}Es^{\alpha}OH^{\alpha}$) with a cone conformation. To give **4a**($Bzl^{\alpha}Es^{\beta}Es^{\alpha}Es^{\beta}$) with a 1,3-alternate conformation as a final product, the OH groups must rotate when the third and the fourth substituent enter. The result is different from the introduction of four esters into **1a** in which the rotation occurs only when the fourth substituent enters. We consider that Cs^+ can act as a template ion, although weakly, for the reaction of $OH^{\alpha}Es^{\alpha}OH^{\alpha}Es^{\alpha}$ and ethyl bromoacetate to selectively give **5a**($OH^{\alpha}Es^{\alpha}Es^{\alpha}Es^{\alpha}$) with a cone conformation because the disubstituted cavity of this calix[4]arene is not so rigid as the tetrasubstituted cavity of cone-**2a** and can interact with Cs^+ in an induced-fit manner. In contrast, the interaction of Cs^+ and **6a**($Bzl^{\alpha}OH^{\alpha}Es^{\alpha}OH^{\alpha}$) (one ester is replaced with a benzyl) is not so strong as that in $OH^{\alpha}Es^{\alpha}OH^{\alpha}Es^{\alpha}$ and the template effect should be weakened. This is why **6a**($Bzl^{\alpha}OH^{\alpha}Es^{\alpha}OH^{\alpha}$) gives the Es-inverted **4a**($Bzl^{\alpha}Es^{\beta}Es^{\alpha}Es^{\beta}$).

Two-Phase Solvent Extraction of Alkali Metal Cations. Solvent extraction and transport of alkali metal cations by a calix[*n*]arene family was first investigated by Izatt et al. by using unmodified calix[*n*]arenes.[26,27] Their results showed that all calix[*n*]arenes (*n* = 4, 6, and 8) exhibit the Cs^+ selectivity.[26,27] It was later found by Ungaro et al.,[7] McKervey et al.,[9,10] and Chang et al.[8] that calix[*n*]arenes can be derived to neutral ligands by introduction of ester or amide groups into the OH groups. They demonstrated that the metal selectivity is dependent on the calix[n]arene ring size, and in particular, calix[4]aryl acetates and acetamides with a cone conformation show remarkably high Na^+ selectivity.[7-11] This clearly indicates that the ionophoric cavity composed of four esters or amides fits the size of Na^+ ion. However, investigations of ionophoric calix[4]arenes have so far been limited to a "cone" family. More recently, we found, quite accidentally, that one can synthesize conformational isomers other than cone from calix[4]arene, the ionophoric cavity of which is composed of two esters and two pyridines.[12] We established through two-phase solvent extraction that the metal selectivity can be changed not only by the change in the ring size but also by the conformational change.[12] The finding tempted us to synthesize all conformational isomers of **2**, the most well-known neutral ligands derived from calix[4]arene.

Solvent extraction of alkali metal cations with picrate ion into dichloromethane was performed at 25 °C. The results were summarized in Table III. As described in the Experimental Section, the physical properties of the conformational isomers of **2** were very similar to each other, so that the isolation of each isomer was very difficult. We thus utilized the fractional recrystallization method in the presence of $NaClO_4$. From a mixture of partial-cone-**2a** and 1,2-alternate-**2a**, partial-cone-**2a** precipitated as its $NaClO_4$ complex in preference to 1,2-alternate-**2a**. From a mixture of partial-cone-**2a** and 1,3-alternate-**2a**, 1,3-alternate-**2a** precipitated as its $NaClO_4$ complex in preference to partial-cone-**2a**. From the results one can predict the order of the Na^+ affinity to be 1,3-alternate-**2a** > partial-cone-**2a** > 1,2-alternate-**2a**. It is seen from Table III that cone-**2a** shows the highest affinity toward Na^+ among four conformational isomers but the order of Na^+ affinity for the residual three isomers is exactly in line with this prediction.

Table III. Percent Extraction of Alkali Metal Picrates in CH_2Cl_2 at 25 °C[a]

calixarene	extractability (Ex%)			
	$M^+ = Li^+$	Na^+	K^+	Cs^+
cone-**2a**	17.6	100	86.1	24.6
partial-cone-**2a**	5.2	62.1	94.3	49.9
1,2-alternate-**2a**	0	22.1	70.0	54.0
1,3-alternate-**2a**	1.5	88.8	100	98.9
cone-**2b**	0	97.0	27.4	4.0
1,3-alternate-**2b**	0	23.9	87.1	54.2

[a] Aqueous phase (5 mL) contains M^+Pic^- (2.50×10^{-4} M), MOH (0.10 M), MCl (0.50 M). Organic phase (CH_2Cl_2, 5 mL) contains calixarene ionophores (2.50×10^{-4} M).

As is already known,[7-11] cone-**2a** showed Na^+ selectivity. In contrast, the residual three conformers showed the K^+ selectivity, indicating that the ionophoric cavities are more or less enlarged. In 1,3-alternate-**2a**, the ionophoric cavity is composed of two ester groups. The X-ray crystallographic studies[28-30] and the computational studies[22,23] established that the dihedral angles between the four phenol units and the mean plane of the four methylene carbons are close to 90°, resulting in the parallel orientation of the four phenol units. In this conformation, therefore, the distance between the two 1,3-esters is longer than that in cone-**2a**. From the X-ray crystallographic studies of an analogous calix[4]arene with a 1,3-alternate conformation,[30] we can calculate the distances between the two carbonyl oxygens and the two ethereal oxygens to be 4.95 and 5.06 Å, respectively, when the ester carbonyl groups are turned inward. When a metal cation is bound into this cavity, the metal–oxygen distances are estimated to be 2.77–2.95 Å. These distances are longer than those for O–Na^+ (2.38–2.60 Å)[14e] but comparable with those for O–K^+ (2.71–2.74 Å).[24] This is why 1,3-alternate-**2a** shows the K^+ selectivity. Table III shows, however, that 1,3-alternate-**2a** has high extractability for Cs^+. As mentioned above, 1,3-alternate conformers are sterically less crowded. This will allow the rotation of the ester groups to provide a larger ionophoric cavity for Cs^+.

It is known that the cavity constructed on the partial-cone skeleton shows poor ionophoricity.[12] This is probably due to a phenol unit distal to an inverted phenol unit, which is flattened into the annulus and sterically interferes with the binding of a metal cation.[12] In the energy-optimized partial-cone conformation two phenol units proximal to an inverted phenol unit are more or less parallel to each other[22,23] like those in the 1,3-alternate conformation. The characteristic structure of the partial-cone conformation is also ascertained by the X-ray crystallographic studies.[12,28,29] How does partial-cone-**2a** interact with metal cations? As shown in Figure 2, the ^1H NMR spectrum of the $ArCH_2Ar$ methylene protons in partial-cone-**2a** consist of two pairs of doublets, one with

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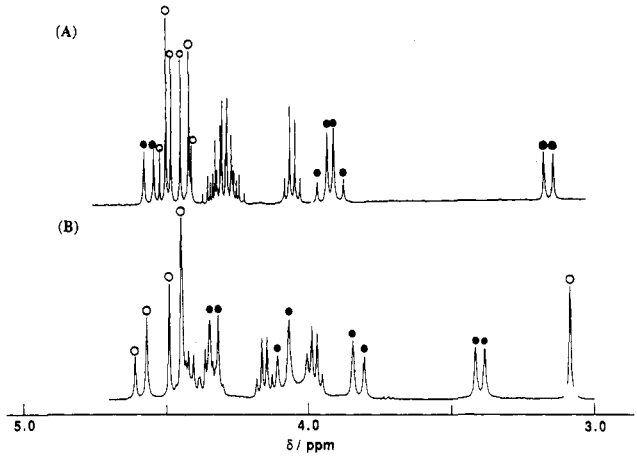

Figure 2. Partial ^1H NMR spectra of the $ArCH_2Ar$ (filled circles) and OCH_2CO methylene protons (open circles) in partial-cone-**2a** (1.0×10^{-3} M), $CDCl_3$, 25 °C, 400 MHz, (A) in the absence of sodium perchlorate and (B) in the presence of sodium perchlorate (1.0×10^{-3} M).

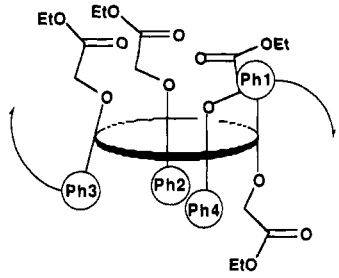

Figure 3. Schematic representation of the metal-induced rotation.

the large chemical shift difference (assignable to $ArCH_2Ar$ in a syn conformation: $\Delta\delta = 1.37$ ppm) and another with the small chemical shift difference (assignable to $ArCH_2Ar$ in an anti conformation: $\Delta\delta = 0.06$ ppm). When $NaClO_4$ was added, $\Delta\delta$ for the former doublet was decreased while that for the latter doublet was increased. Since $\Delta\delta$ serves as a measure of the "flattening",[13b] the spectral data imply that, as shown in Figure 3, Ph3 (so-called "flattened" phenol unit) is more flattened and Ph1 (inversed phenol unit) stands up.[31] In the OCH_2CO methylene protons one singlet resonance shifts to unusually high magnetic field upon addition of the metal cation (Figure 2). This peak is assigned to the OCH_2CO methylene protons in Ph1 because it moves into the shielding area of Ph2 and Ph4 (Figure 3). These results show a metal-binding manner occurring in partial-cone-**2a**: a metal cation is flanked by the two OCH_2CO groups in Ph2 and Ph4 and the OCH_2CO group in Ph3 is flattened so that it can coordinate to the metal cation. As a consequence, Ph1 must stand up to the opposite direction.

To the best of our knowledge, there exists only one example in which the X-ray structure of the 1,2-alternate conformation has been successfully analyzed.[28] It is seen from the ORTEP view that all of the four phenol units are considerably flattened. The theoretical calculation of 25,26,27,28-tetramethoxycalix[4]arene with a 1,2-alternate conformation predicts that the dihedral angles between the phenol units and the mean plane of the four $ArCH_2Ar$ methylene carbons are 63–64°.[23] Thus, the low extractability is ascribed to two defects of the ionophoric cavity: (i) the flattened ester groups do not act as efficient ligands to tweeze a metal cation and (ii) the ion-binding ability of an ionophore which tweezes a metal cation with two proximal ligands (90° angle) is not so strong as that which tweezes a metal cation with two distal ligands (180° angle) as in a 1,3-alternate conformation. At present, it is difficult to further specify why 1,2-alternate-**2a** shows the K^+ selectivity.

(31) The rotation of Ph2 and Ph4 might induce the similar chemical shift change.

Table IV. Bathochromic Shifts ($\Delta\lambda$) and Association Constants (K_{ass}) of Alkali Picrates (M^+Pic^-)[a]

	$\Delta\lambda$ (nm)			log K_{ass} (M^{-1})		
ionophore	$M^+ = Na^+$	K^+	Cs^+	$M^+ = Na^+$	K^+	Cs^+
cone-**2a**	31	2	0	3.95	3.08	1.60[c]
partial-cone-**2a**	5	7	12	4.26	3.52	2.12
1,2-alternate-**2a**	*b*	*b*	*b*	*b*	*b*	*b*
1,3-alternate-**2a**	8	28	2	4.10	4.98	4.41

[a] 30 °C, $[M^+Pic^-] = 5.00 \times 10^{-6}$ M, [**2a**] = 0–5×10^{-4} M. The λ_{max} values of M^+Pic^- in the absence of the ionophore are 351 nm for Na^+, 357 nm for K^+, and 362 nm for Cs^+. [b] The spectral change was too small to determine the K_{ass} accurately. [c] The K_{ass} was determined from the decrease in the absorbance at 362 nm.

Stoichiometry and Association Constants. We previously reported that cone-**2a** forms 1:1 complexes with all alkali metal cations and does not form 1:2 metal/calixarene sandwich complexes as in metal/crown complexes.[11] This ionophoric characteristic of the calixaryl esters is attributed to the deep encapsulation of alkali metal cations in the cavity. Inoue et al.[32] suggested an interesting idea that the bathochromic shift of the absorption band of the picrate anion, extracted into the organic phase with a macrocyclic ligand from aqueous metal picrate solutions, serves as a convenient measure for evaluating the ion pair tightness in solution. We thus plotted the new absorption maxima (if any) induced by added **2a** against the **2a** concentration. From the plots one can estimate the stoichiometry of the complexes and the association constants (K_{ass}). The data taken in THF are summarized in Table IV.

The spectral change induced by 1,2-alternate-**2a** was too small to estimate the stoichiometry and the K_{ass}. As the two ester ligands on the same ring edge are arranged in 90°, it cannot construct an ionophoric "cavity" enough to make a solvent-separated ion pair. The remaining three isomers induced the distinct spectral change. It was confirmed from the mole ratio plots that these three isomers basically form 1:1 complexes with alkali metal cations. In Table IV, $\Delta\lambda$ denotes the bathochromic shift obtained in the presence of excess **2a** (i.e., at a plateau of [**2a**] vs $\Delta\lambda$ plots). The shifts observed for cone-**2a** + Na^+ (31 nm) and 1,3-alternate-**2a** + K^+ (28 nm) are comparable with that of cryptand 222 + Na^+ (31 nm)[8] and greater than that of 18-crown-6 + K^+ (13 nm).[8] The results show that the ionophoric cavities in these isomers lie deeply in the molecule and form solvent-separated ion pairs with alkali picrates.

The K_{ass} values were determined using the Benesi–Hildebrand equation for a 1:1 complex.[33] Although the solvent (THF) used herein is different from that used in two-phase solvent-extraction (dichloromethane), the orders of the K_{ass} for cone-**2a** and 1,3-alternate-**2a** are in line with those of the extractability: $Na^+ > K^+ > Cs^+$ for cone-**2a** and $K^+ > Cs^+ > Na^+$ for 1,3-alternate-**2a**. It is seen from Table IV, however, that 1,3-alternate-**2a** shows a broad ion-selectivity (log K_{ass} = 4.10–4.98) whereas cone-**2a** shows a sharp selectivity toward K^+. In partial-cone-**2a**, the order for Na^+ and K^+ is different between the K_{ass} and the ex-

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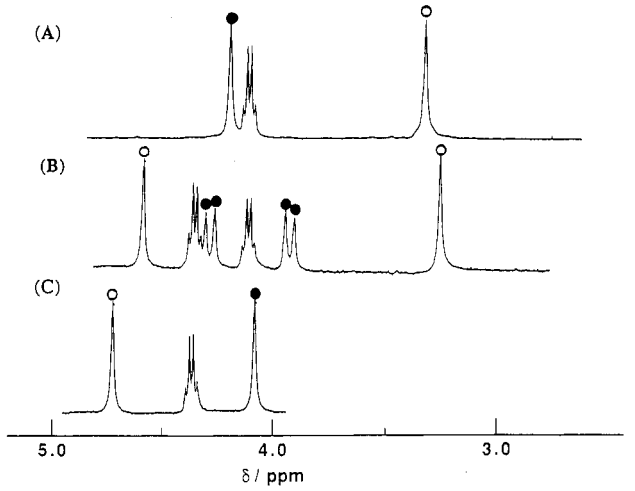

Figure 4. Partial ^1H NMR spectra of the $ArCH_2Ar$ (filled circles) and OCH_2CO methylene protons (open circles) in 1,3-alternate-**2a** (5×10^{-4} M), $CDCl_3$:CD_3OD = 1:1 v/v, −50 °C, 400 MHz, (A) in the absence of sodium picrate, (B) in the presence of 1 equiv of sodium picrate, and (C) in the presence of 10-fold equiv of sodium pictate.

tractability. This is probably due to the difference in the solvent.

^1H NMR Spectra of Metal Complexes. The above spectral studies using alkali picrates showed that cone-, partial-cone-, and 1,3-alternate-**2a** form 1:1 complexes. However, 1,3-alternate-**2a** has two equivalent metal-binding sites and therefore may result in an additional 2:1 metal/calixarene complex. Also, the K_{ass} for 1,2-alternate-**2a** could not be determined by the spectroscopic method. To supplement these missing results we studied the metal–calixarene interactions using ^1H NMR spectroscopy. As shown in Figure 4A, the $ArCH_2Ar$ methylene protons in 1,3-alternate-**2a** appeared as a singlet resonance at 4.16 ppm ($CDCl_3$:CD_3OD = 1:1 v/v, −50 °C). This is due to high D_{2d} symmetry of 1,3-alternate-**2a**. It is also worthy to mention that the OCH_2CO methylene protons appear at unusually high magnetic field (3.30 ppm: compare with 4.86 ppm for cone-**2a**). When 1 equiv of sodium picrate was added, the $ArCH_2Ar$ methylene protons split into a pair of doublets and two of four OCH_2CO methylene groups shifted to lower magnetic field (Figure 4B). The split is readily attributed to metal-induced asymmetry. In 1,3-alternate-**2a** an OCH_2CO group and a benzene ring are arranged alternately. The cavity edge is not so crowded.[23] Thus, the OCH_2CO groups can rotate freely, so that the carbonyl groups may be turned outward to reduce the electrostatic repulsion. In such a conformation, the OCH_2CO methylene protons lie in some probability in the shielding area of the neighboring benzene rings. When the metal cation comes in, the carbonyl groups are turned inward to bind the metal cation and the methylene groups are turned outward. In this conformation, the OCH_2CO methylene protons lie at the outside of the ring and no longer undergo the shielding effect of the neighboring benzene rings. The conformational change can thus explain the changes in the chemical shift of the OCH_2CO methylene protons. Interestingly, we noticed that when 10-fold equivalents of sodium picrate were added, a new singlet resonance for the $ArCH_2Ar$ methylene protons appeared at 4.06 ppm (Figure 4C). The peak is assignable to a 2:1 metal/calixarene complex with D_{2d} symmetry. From the integral intensity we estimated log K_{ass} for the binding of first Na^+ to be 4.38 and that for the binding of second Na^+ (= [1,3-alternate-**2a**·Na^+_2]/[1,3-alternate-**2a**·Na^+][Na^+]) to be 0.60. The results indicate that the two metal-binding sites in 1,3-alternate-**2a** have the character of the negative allostericity. The behavior is probably related to the electrostatic repulsion which occurs upon the binding of second Na^+.[34]

We also estimated the K_{ass} of K^+ for the formation of a 1:1 complex with 1,3-alternate-**2a** and 1,2-alternate-**2a** from their ^1H NMR spectra: log K_{ass} 5.15 for 1,3-alternate-**2a** and 3.78 for 1,2-alternate-**2a**. The solvent extraction studies (Table III) showed that 1,3-alternate-**2a** has the selectivity toward K^+ over Na^+ and has the Ex% higher than 1,2-alternate-**2a**. As expected from these results, the K_{ass} for 1,3-alternate-**2a** + K^+ is greater by 5.9-fold than that for 1,3-alternate-**2a** + Na^+ and by 23-fold than that for 1,2-alternate-**2a** + K^+. Unfortunately, the formation of a 2:1 metal/calixarene complex could not be evaluated because of the solubility limitation (2-fold equivalents of **2a** (= 5.0×10^{-4} M)).

Concluding Remarks

The present paper demonstrates that all four of the conformational isomers of the calix[4]aryl ester can be synthesized by using metal template effects and a protection–deprotection method. Two-phase solvent extraction of alkali picrates established that the cone isomer shows Na^+ selectivity whereas the remaining three isomers show K^+ selectivity. In particular, 1,3-alternate-**2a** showed high metal ion affinity and formed a 2:1 Na^+/calixarene complex. The results indicate that the ion selectivity in a calix[*n*]aryl ester system can be controlled not only by the ring size but also by conformation. We believe that one can realize the various metal selectivities by the skillful combination of the change in the ring size with the change in the conformational isomerism.

Acknowledgment. We thank Mr. T. Harada (JRDC, Shinkai Chemirecognics Project) for theoretical discussions on the metal-binding process.

(34) The K_{ass} for 1,2-alternate-**2a** + Na^+ could not be determined because of the serious line-broadening.

(35) To represent the stereoisomers derived from calix[4]arene we here introduced $R_1R_2R_3R_4$ for O-substituents and α and β for phenyl inversion. For example, $OH^{\alpha}OH^{\alpha}R_1{}^{\beta}R_2{}^{\beta}$ is proximal R_1, R_2-substituted 1,2-alternate and $Bzl^{\alpha}Es^{\alpha}Es^{\alpha}Es^{\beta}$ is partial-cone in which an ester unit adjacent to the benzyl unit is inverted.

(36) The splitting pattern of the $ArCH_2Ar$ methylene protons for **4a**-($Bzl^{\alpha}Es^{\alpha}Es^{\alpha}Es^{\beta}$) may be similar to that for **4a**($Bzl^{\alpha}Es^{\alpha}Es^{\beta}Es^{\beta}$). We concluded the compound to have a partial-cone conformation on the basis of the following two reasons. (i) Di-O-alkylation of calix[4]arene in the presence of alkali carbonates predominantly yields the cone isomer ($OH^{\alpha}R^{\alpha}OH^{\alpha}R^{\alpha}$),[15] from which the 1,2-alternate isomer cannot be formed. (ii) The CH_3 protons in the ethoxy group shift to higher magnetic field when the adjacent phenol unit is inverted: for example, the δ_H values for partial-cone-**2a** appear at 1.16 (CH_3 in inverted phenyl), 1.30 ($2 \times CH_3$), and 1.33 (CH_3 in flattened phenyl) ppm whereas that for 1,2-alternate-**2a** appears at 1.19 ppm. The δ_H values appearing at 1.13, 1.28, and 1.32 ppm are consistent with **4a**($Bzl^{\alpha}Es^{\alpha}Es^{\alpha}Es^{\beta}$).